NOTCH1 gene

notch 1

Normal Function

The *NOTCH1* gene provides instructions for making a protein called Notch1, a member of the Notch family of receptors. Receptor proteins have specific sites into which certain other proteins, called ligands, fit like keys into locks. Attachment of a ligand to the Notch1 receptor sends signals that are important for normal development of many tissues throughout the body, both before birth and after. Notch1 signaling helps determine the specialization of cells into certain cell types that perform particular functions in the body (cell fate determination). It also plays a role in cell growth and division (proliferation), maturation (differentiation), and self-destruction (apoptosis).

The protein produced from the *NOTCH1* gene has such diverse functions that the gene is considered both an oncogene and a tumor suppressor. Oncogenes typically promote cell proliferation or survival, and when mutated, they have the potential to cause normal cells to become cancerous. In contrast, tumor suppressors keep cells from growing and dividing too fast or in an uncontrolled way, preventing the development of cancer; mutations that impair tumor suppressors can lead to cancer development.

Health Conditions Related to Genetic Changes

Adams-Oliver syndrome

At least 15 mutations in the *NOTCH1* gene have been found to cause Adams-Oliver syndrome, a condition characterized by areas of missing skin (aplasia cutis congenita), usually on the scalp, and malformations of the hands and feet. These mutations are usually inherited and are present in every cell of the body. Some of the *NOTCH1* gene mutations involved in Adams-Oliver syndrome lead to production of an abnormally short protein that is likely broken down quickly, causing a shortage of Notch1. Other mutations change single protein building blocks (amino acids) in the Notch1 protein. These changes are thought to alter the structure of the protein, impairing its ability to function. Loss of Notch1 signaling may underlie blood vessel and heart abnormalities in people with Adams-Oliver syndrome. However, while these types of abnormalities are more common in affected individuals with *NOTCH1* gene mutations than in those with a different gene mutation, some people with Notch1-related Adams-Oliver syndrome do not have blood vessel or heart abnormalities. It is not clear how loss of Notch1 function leads to the scalp and limb abnormalities characteristic of the condition. Researchers suggest these features may be due to abnormal blood vessel development before birth.

critical congenital heart disease

head and neck squamous cell carcinoma

Mutations in the *NOTCH1* gene have been found in about 15 percent of head and neck squamous cell carcinomas (HNSCC). This type of cancerous tumor occurs in the moist lining of the mouth, nose, and throat. *NOTCH1* gene mutations associated with this condition are acquired during a person's lifetime and are found only in tumor cells; these changes are known as somatic mutations. Mutations in the *NOTCH1* gene may reduce or eliminate production of functional Notch1 protein or lead to production of a protein that is unable to participate in cell signaling. Without the tumor suppressor function of the Notch1 protein, cells can grow and divide without control, leading to tumor formation.

other cancers

NOTCH1 gene mutations have been found in other types of cancer, particularly blood cell cancers called T-cell acute lymphoblastic leukemia and chronic lymphocytic leukemia, and a type of lung cancer called non-small cell lung cancer. Unlike in HNSCC (described above), the *NOTCH1* gene mutations found in these cancers abnormally turn on (activate) Notch1 signaling. The increased activity can lead to uncontrolled cell growth and division, which can result in the development of cancer. Researchers are working to understand how both activating and inactivating *NOTCH1* gene mutations can lead to cancer development.

other disorders

Mutations in the *NOTCH1* gene can impair normal heart development before birth, causing abnormalities of the heart and related structures. One such abnormality occurs in the valve that connects the aorta to the heart (the aortic valve). The aorta is the large blood vessel that distributes blood from the heart to the rest of the body. The aortic valve normally has three flaps, or cusps, that open to let blood leave the heart and come together to prevent blood from reentering the heart. However, in about 1 to 2 percent of people, the aortic valve has only two flaps, which is known as a bicuspid aortic valve. *NOTCH1* gene mutations appear to be involved in 4 to 10 percent of bicuspid aortic valve cases.

Individuals with a bicuspid aortic valve are at a higher than normal risk of developing other aortic abnormalities, such as a bulge in the wall of the aorta (thoracic aortic aneurysm) or a sudden tearing of the layers in the aorta wall (aortic dissection). In addition, accumulation of calcium on the aortic valve can occur in people with a bicuspid aortic valve. Researchers suspect that *NOTCH1* gene mutations also play a role in the development of thoracic aortic aneurysms and in calcification of the valve.

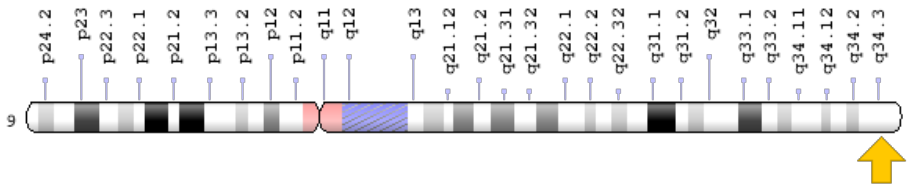
NOTCH1 gene mutations are also involved in critical congenital heart disease. Individuals with this condition have one or more specific heart abnormalities that

affect the flow of blood into, out of, or through the heart. Some of the heart defects involve structures within the heart itself, such as the two lower chambers of the heart (the ventricles) or the valves that control blood flow through the heart. Others affect the structure of the large blood vessels leading into and out of the heart (including the aorta and pulmonary artery). Still others involve a combination of these structural abnormalities.

Chromosomal Location

Cytogenetic Location: 9q34.3, which is the long (q) arm of chromosome 9 at position 34.3

Molecular Location: base pairs 136,494,433 to 136,545,786 on chromosome 9 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- AOS5
- AOVD1
- hN1
- neurogenic locus notch homolog protein 1
- neurogenic locus notch homolog protein 1 preproprotein
- Notch homolog 1, translocation-associated
- TAN1
- translocation-associated notch protein TAN-1

Additional Information & Resources

Educational Resources

- Molecular Cell Biology (fourth edition, 2000): Proto-Oncogenes and Tumor-Suppressor Genes
  https://www.ncbi.nlm.nih.gov/books/NBK21662/

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28NOTCH1%5BTI%5D%29+OR+%28notch+1%5BTI%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+360+days%22%5Bdp%5D

OMIM

- AORTIC VALVE DISEASE 1
  http://omim.org/entry/109730
- LEUKEMIA, ACUTE LYMPHOBLASTIC
  http://omim.org/entry/613065
- LEUKEMIA, CHRONIC LYMPHOCYTIC
  http://omim.org/entry/151400
- NOTCH, DROSOPHILA, HOMOLOG OF, 1
  http://omim.org/entry/190198

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/NOTCH1ID30ch9q34.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=NOTCH1%5Bgene%5D
- HGNC Gene Family: Ankyrin repeat domain containing
  http://www.genenames.org/cgi-bin/genefamilies/set/403
- HGNC Gene Symbol Report
  http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=7881
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/4851
- UniProt
  http://www.uniprot.org/uniprot/P46531

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